COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Building Innate Warfighter Resiliency Against CB Threats Via The Gut Microbiome

Katherine Besse MIT Lincoln Laboratory **Todd Thorsen** MIT Lincoln Laboratory **Isabel Smokelin** MIT Lincoln Laboratory **James Comolli** MIT Lincoln Laboratory **Johanna Bobrow** MIT Lincoln Laboratory **David Drew** Massachusetts General Hospital **David Walsh** MIT Lincoln Laboratory

A resilient gut microbiome can mitigate warfighter performance decrements to low level chemical, biological or radiation (CBR) exposure. However, human gut microbiome studies today are almost exclusively limited to animal models due to a lack of available in vitro tools capable of recreating the complex gut environment. Furthermore, the over-simplification of existing in vitro tools reduces the utility and predictive value of the data they generate. Building upon the growing MITLL expertise in 3D printing, we have been designing and prototyping milliliter-scale ArtGut systems with 90 independent chambers that emulate the gas gradients found in the colon that enable the co-culture of microbiome communities with diverse oxygen requirements. These initial prototyped parts, 3D-printed in rigid photosensitive urethane-based materials, function as bioreactors in our ongoing study to investigate the impact of environmental perturbations on key metabolic profiles of polymicrobial cultures. Dysbiosis triggered by a change in environmental conditions (such as exposure to chemical toxins) can have nuanced, but potentially serious effects on the host. Current microbiome studies on toxicants rely on methods such as 16S sequencing and short-chain fatty acid (SCFA) analysis. Using ArtGut as the primary culture tool, we are taking this analysis to the next level to identify key metabolic pathways impacted by dysbiosis. Using back-end tools like flow injection analysis electrospray ionization mass spectrometry (FIA ESI MSMS) to analyze the culture samples, we are able to detect microbiome metabolites at single micromolar concentrations, orders of magnitude lower than the millimolar concentrations typically observed in the colon. Combining this data with metatranscriptomic genetic analysis of the microbiome samples pre- and post-exposure to chemical toxins provides a detailed snapshot of key pathways activated, and allows the benchtop researcher to investigate potential mitigation treatments in subsequent ArtGut experiments.